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CYCLIZATION OF 6-BROMO-1,2-EPOXYHEXANE PROMOTED BY METAL-HALOGEN EXCHANGE: UNEXPECTED REGIOSELECTIVITY

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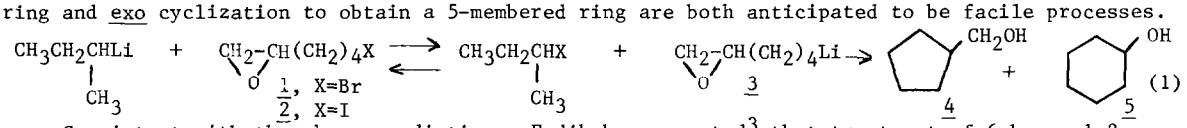
SUMMARY: Treatment of 6-bromo-1,2-epoxyhexane (1) with one equivalent of sec-butyllithium afforded a 95:5 mixture of cyclopentylmethanol (4): cyclohexanol in approximately 40% yield. An analogous tandem metal-halogen exchange/cycloalkylation process using the oxirane derivative (2) of 6-iodo-1-hexene gave virtually the same mixture of alcohols in >60% yield.

During the past decade considerable effort has been directed toward determining the regioselectivity in intramolecular alkylations involving epoxides.[1] As part of our continuing interest in this area, we decided to examine cycloalkylation reactions undergone by organometallic derivatives (e.g., 3) of haloepoxides. A substrate such as 3 seemed particularly intriguing since, according to Baldwin's rules[2] for ring closure, endo cyclization to furnish a 6-membered ring and exo cyclization to obtain a 5-membered ring are both anticipated to be facile processes.



Consistent with the above predictions, Erdik has reported[3] that treatment of 6-bromo-1,2-epoxyhexane (1) with an excess of magnesium in the presence of 0.5 molar equivalent of cuprous iodide afforded a 4:1 mixture of 5:4 in 34% yield. Similar treatment of 1 with lithium and CuI in tetrahydrofuran gave cyclohexanol as the sole cyclization product in approximately 25% yield.[4] A related study[5] involving cis- and trans-1-bromo-2-(3-butenyl)cyclopropane oxide augments Erdik's results in that formation of the 6-membered ring was reported to be favored. In contrast, another cyclization, involving the formation of a heterocycle from an aryl bromide, was reported[6] to afford only the 5-membered ring product.

At the onset of this project, we decided to examine the possibility of promoting cycloalkylation of haloepoxides such as 1 by lithium-halogen exchange.[7] Not surprisingly, since similar reactions have been reported[7] to be unfavorable for 1° alkyl halides, treatment of epoxybromide 1[8] with n-butyllithium (1 equiv) in ether-hexane at -78°C afforded a horrendous mixture of products containing little, if any, of the desired cyclization product (4 and/or 5). To our amazement, similar treatment of 1 with sec-butyllithium[9] (1 equiv) at -78°C led to a facile metal-halogen exchange[10] and a considerably slower cycloalkylation involving the derived organolithium (3). Nevertheless, after 3 hours at -78°C, a 19:1 mixture[11] of 4:5 could be isolated in approximately 20% yield after chromatographic purification. A substantially improved yield (∿40%) of this same mixture of alcohols was realized when the cycloalkylation was conducted at 0°C. More importantly, from a preparative viewpoint, application of this methodology to iodoepoxide 2[12] proceeded smoothly, affording a 24:1 mixture of 4:5 in >60% yield!

In view of the disparity of our results with the regioselectivity previously observed by Erdik,[3,4] we examined the affect of CuI on this "metal-halogen exchange" promoted cycloalkylation. When the latter process involving bromoepoxide 1 was conducted[13] in the presence

of CuI(0.1 molar equiv), surprisingly no significant increase (16:1 ratio of 4 to 5) in the formation of cyclohexanol was detected.

A more detailed study of this cyclization methodology, including its scope, is presently being initiated and results will be reported in a future article.

Cyclization Procedure: To a solution of 2.00 mmoles of haloepoxide (1 or 2) in 4.0 mL of anhydrous ether, cooled to -78°C (external temperature, dry ice/acetone bath) and maintained under a nitrogen atmosphere, was added dropwise rapidly (via syringe through a rubber septum) a 0.50M solution of sec-butyllithium[9,14] in cyclohexane (4.0mL). After stirring this mixture at -78°C for 15 min, the flask was placed in an ice-water bath at 0°C. The mixture was subsequently stirred for an additional 2 h at that temperature, after which the reaction was quenched by addition of 5 mL of saturated aqueous NH_4Cl. The product was isolated by dilution of this mixture with 35 mL of brine and extraction with ether.[15] Obtention of the mixture of C_6- alcohols derived from this cyclization was effected by chromatography on Florisil (15 mL, 60-100 mesh, gradient elution using pentane-ether[16]). Subsequent NMR[17] and GC analysis (6ft x 1/8 in column packed with 10% FFAP on 80/100 mesh Chromosorb W-AW, 125°C, flow: 15 mL/min) indicated the alcohol product to be cyclopentylmethanol (4) (t_R = 6.2 min, ~ 95%), accompanied by a minor amount (~ 5%) of cyclohexanol[18] (t_R = 5.1 min) as the only other detectable component.

REFERENCES AND NOTES

1. See pp 2351-2355 in a review by A.S. Rao, S.K. Paknikar, and J.G. Kirtane, Tetrahedron, 39, 2323-2367 (1983) and references therein.
2. J.E. Baldwin, J. Chem. Soc., Chem. Commun., 734 (1976).
3. E. Erdik, Chim. Acta Turc., 9, 353 (1981).
4. E. Erdik, Chem. Abstr., 93, 25962y (1980).
5. L.A. Last, R. Fretz, and R.M. Coates, J. Org. Chem., 47, 3211 (1982).
6. C.K. Bradsher and D.C. Reames, J. Org. Chem., 43, 3800 (1978).
7. For a review see: R.G. Jones and H. Gilman, Org. React., 6, 339 (1951).
8. This epoxide (1) was prepared by treatment of 6-bromo-1-hexene (Wiley Organics, Inc., Columbus, Ohio, USA) with m-chloroperbenzoic acid in dichloromethane.
9. Available from Aldrich Chemical Co., Milwaukee, WI. USA.
10. Quenching this reaction after 15 minutes at -78°C by addition of methanol indicated that exchange had occurred since <10% of the starting bromoepoxide (1) could be recovered. However, very little cycloalkylation had occurred under these conditions.
11. This ratio was determined by GC analysis of the reaction product.
12. Iodoepoxide 2 was prepared by treatment (18h) of the corresponding bromide (1) with NaI (1.5 equiv) in refluxing acetone (1M solution) containing a catalytic amount of $CaCO_3$. Satisfactory elemental analysis (C,H,I) was obtained for this novel compound: bp 65-83°C (bath temp, 0.40mm).
13. In this experiment, CuI (34mg, 0.18 mmol) was added to the reaction mixture after the latter was transferred from a bath at -78°C to one at 0°C (see the cyclization procedure).
14. The molarity of this reagent was determined by titration with 1,3-diphenyl-2- propanone tosylhydrazone. For details concerning the use of the latter indicator, see: M.F. Lipton, C.M. Sorensen, A.C. Sadler, and R.H. Shapiro, J. Organometal. Chem., 186, 155 (1980).
15. The ether extracts were washed with saturated brine (2 x 35mL), dried ($MgSO_4$), and filtered prior to removal of most of the solvent by fractional distillation (760mm) to minimize loss of the volatile C_6- alcohols. The last traces of solvent were removed using a rotary evaporator (bath temp <20°C).
16. Removal of the non C_6-alcohol components was accomplished by elution with pentane-1% ether (3 x 15mL), followed by pentane-2% ether (1 x 15 mL). The desired alcohol product (4 and 5) was then quickly recovered by elution with pentane-16% ether (5 x 15mL). NMR analysis of the initial fractions in this chromatography indicated the presence of minor amounts of unreacted starting material, accompanied by other components containing a terminal epoxide moiety. Due to the apparent complexity of this mixture, however, it was not further characterized.
17. The ^1H NMR spectrum of the major product (4) exhibited a doublet (J=6Hz) at 3.52 δ ($C\underline{H}_2OH$) and was identical to that published for alcohol 4 in The Aldrich Library of NMR Spectra.
18. This component's identity was verified by coinjection with an authentic sample of cyclohexanol.

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